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 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  AUG 09   INSPEC enhanced with 1898-1968 archive
 NEWS  4  AUG 28   ADISCTI Reloaded and Enhanced
 NEWS  5  AUG 30   CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS  6  SEP 11   CA/CAplus enhanced with more pre-1907 records
 NEWS  7  SEP 21   CA/CAplus fields enhanced with simultaneous left and right
                   truncation
 NEWS  8  SEP 25   CA(SM)/CAplus(SM) display of CA Lexicon enhanced
 NEWS  9  SEP 25   CAS REGISTRY(SM) no longer includes Concord 3D coordinates
 NEWS 10  SEP 25   CAS REGISTRY(SM) updated with amino acid codes for pyrrolysine
 NEWS 11  SEP 28   CEABA-VTB classification code fields reloaded with new
                   classification scheme
 NEWS 12  OCT 19   LOGOFF HOLD duration extended to 120 minutes
 NEWS 13  OCT 19   E-mail format enhanced
 NEWS 14  OCT 23   Option to turn off MARPAT highlighting enhancements available
 NEWS 15  OCT 23   CAS Registry Number crossover limit increased to 300,000 in
                   multiple databases
 NEWS 16  OCT 23   The Derwent World Patents Index suite of databases on STN
                   has been enhanced and reloaded

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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=> interferon (p) response
L1       57295 INTERFERON (P) RESPONSE

=> deficien3
 75% OF LIMIT FOR TOTAL ANSWERS REACHED
L2     9442219 3

=> L1 and l2
L3       15930 L1 AND L2

=> defect and L3
L4         265 DEFECT AND L3

=> cancer and L3
L5        1339 CANCER AND L3

=> neoplasm and l4
L6          19 NEOPLASM AND L4

=> tumor  and L4
L7          77 TUMOR AND L4

=> leukemia and l4
L8          15 LEUKEMIA AND L4

=> D L8 IBIB ABS 1-8

L8   ANSWER 1 OF 15  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:59829  CAPLUS
DOCUMENT NUMBER:          142:133060
TITLE:                    Liposome complexes with ligands for pattern
                          recognition receptors enhance the immune response
INVENTOR(S):              Dow, Steven W.; Fairman, Jeffery
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 46 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    -------------------      --------
     US 2005013812         A1    20050120    US 2003-621254           20030714
     AU 2004262523         A1    20050217    AU 2004-262523           20040608
     CA 2532140            AA    20050217    CA 2004-2532140          20040608
     WO 2005013891         A2    20050217    WO 2004-US18363          20040608
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP,. KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
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SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1648379 A2 20060426 EP 2004-776412 20040608

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR

PRIORITY APPLN. INFO.: US 2003-621254 A 20030714

WO 2004-US18363 W 20040608

AB The authors disclose methods for enhancing immune activation which are effective for eliciting both a systemic, non-antigen specific immune response and a strong antigen-specific immune response in a mammal. In one example, an enhanced immune response is observed for liposome-peptide-nucleic acid complexes. The method may be effective for protecting a mammal from a disease including cancer, a disease associated with allergic inflammation, an infectious disease, or a condition associated with a deleterious activity of a self-antigen.

L8 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:486707 CAPLUS

DOCUMENT NUMBER: 131:252207

TITLE: Retinoic acid resistance in NB4 APL cells is associated with lack of interferon α synthesis stat1 and p48 induction

AUTHOR(S): Pelicano, Luis; Brumpt, Caren; Pitha, Paula M.; Chelbi-Alix, Mounira K.

CORPORATE SOURCE: CNRS, UPR 9051, Hopital St. Louis, Paris, Paris, 75475, Fr.

SOURCE: Oncogene (1999), 18(27), 3944-3953
CODEN: ONCNES; ISSN: 0950-9232

PUBLISHER: Stockton Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In the t(15;17) acute promyelocytic leukemia (APL), all-trans-retinoic (RA) treatment induces maturation leading to clin. complete but not durable remission, as RA resistance develops in the treated patients as well as in vitro. RA and interferons (IFNs) are known inhibitors of proliferation in various cells including those from APL. In this report, we show that they can act cooperatively to inhibit growth and to induce differentiation of NB4 cells but not of two RA-resistant NB4 derived cell lines, NB4-R1 and NB4-R2. However, the resistant cell lines respond to IFN. In NB4 cells, RA increases the expression of Stat1, p48 and IRF-1, three transcription factors playing a central role in the IFN response and induces the synthesis and the secretion of IFNα. RA-induced IFNα seems to play a role in inhibition of NB4 cell growth but not in their differentiation. In the resistant cells, NB4-R1 and NB4-R2, both the induction of IFN and the increase of Stat1 and p48 expression by RA are completely blocked. In contrast, IRF-1 mRNA and protein expressions are induced in the three cell lines. This suggests that increase of IRF-1 expression is not sufficient for IFN induction. Our results identify some defects linked to RA-resistance in APL and support the hypothesis that RA-induced Stat1 expression and IFN secretion may be one of the mechanisms mediating growth inhibition by RA.

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:288679 CAPLUS

DOCUMENT NUMBER: 131:86406

TITLE: CCAAT/enhancer binding protein ε is critical for effective neutrophil-mediated response to inflammatory challenge

AUTHOR(S): Lekstrom-Himes, Julie; Xanthopoulos, Kleanthis G.

CORPORATE SOURCE: Clinical Gene Therapy Branch, National Human Genome Research Institute, National Institutes of Health,

Bethesda, MD, USA
SOURCE: Blood (1999), 93(9), 3096-3105
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Targeted mutation of CCAAT/enhancer-binding protein (C/EBP) ε in mice results in early death, primarily due to spontaneous infection with Pseudomonas aeruginosa. Functional anal. of C/EBPε-deficient neutrophils, in an in vivo model of peritoneal inflammation, shows multiple defects. Reduction of phagocytotic killing by C/EBPε-deficient neutrophils is a result of decreased uptake of opsonized bacteria as well as little to no expression of secondary granule proteins. Abnormalities in neutrophil migration detected in a chemical peritonitis model are likely secondary to abnormal CD11b integrin and L-selectin expression on C/EBPε-deficient neutrophils. Alterations in neutrophil cytokine expression in response to inflammation show decreased levels of interleukin-1 receptor antagonist (IL-1Ra) and increased levels of tumor necrosis factor-α (TNF-α) expression by C/EBPε-deficient neutrophils. Addnl., TNF-α expression is increased in nonactivated, circulating C/EBPε-deficient neutrophils. Overall, C/EBPε-deficient neutrophils are severely functionally impaired, evoking an abnormal microenvironment, which may contribute to the loss of normal responses to inflammatory stimuli. Similarities between the C/EBPε-deficient mouse model and the human disease, specific granule deficiency, will be discussed.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:171277 CAPLUS
DOCUMENT NUMBER: 130:336539
TITLE: The Jak-STAT pathway: cytokine signaling from the receptor to the nucleus
AUTHOR(S): Heim, Markus H.
CORPORATE SOURCE: Department of Research, University Hospital Basel, Basel, 4031, Switz.
SOURCE: Journal of Receptor and Signal Transduction Research (1999), 19(1-4), 75-120
CODEN: JRETET; ISSN: 1079-9893
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 239 refs. The Jak-STAT pathway was originally discovered through the study of interferon induced intracellular signal transduction. Meanwhile, a large number of cytokines, hormones and growth factors have been found to activate Jaks and STATs. Jaks (Janus Kinases) are a unique class of tyrosine kinases that associate with cytokine receptors. Upon ligand binding, they activate members of the Signal Transducers and Activators of Transcription (STAT) family through phosphorylation on a single tyrosine. Activated STATs form dimers, translocate to the nucleus, bind to specific response elements in promoters of target genes, and transcriptionally activate these genes. Both pos. and neg. regulations of the Jak-STAT pathway have been identified. In a pos. feedback loop, interferons transcriptionally activate the genes for components of the interferon stimulated gene factor 3 (ISGF3). A number of cytokines that activate the Jak-STAT pathway, e.g. IL-6, IL-4, LIF, G-CSF, have been shown to upregulate the expression of SOCS-JABs-SSIs, a recently discovered class of STAT inhibitors. Targeted disruption of genes for a number of Jaks and STATs in mice have revealed specific biol. functions for many of them. Although most of the STATs are activated in cell culture by many different ligands, STAT knockout mice mostly show defects in a single or a few cytokine dependent processes. STAT1 knockout mice

have an impaired interferon signaling, STAT4 knockouts impaired IL-12 signaling, STAT5a knockouts impaired prolactin signaling, STAT5b knockouts impaired growth hormone signaling, and STAT6 knockout impaired IL-4 and IL-13 signaling. Defects in the Jak-STAT pathway have already been identified in a number of human diseases. Prominent amongst them are leukemias, lymphomas and inherited immunodeficiency syndromes. It can be expected that addnl. Jak-STAT related diseases will be identified over the next years. To date, specific STAT inhibitory drugs are not known, but a number of specific protein-protein interactions in the Jak-STAT pathway are potential targets for pharmaceutical interventions.

REFERENCE COUNT: 112 THERE ARE 112 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:232041 CAPLUS
DOCUMENT NUMBER: 118:232041
TITLE: IL-4 attenuates the transcriptional activation of both IFN-α- and IFN-γ-induced cellular gene expression in monocytes and monocytic cell lines
AUTHOR(S): Larner, Andrew C.; Petricoin, Emanuel F.; Nakagawa, Yoichi; Finbloom, David S.
CORPORATE SOURCE: Div. Cytokine Biol., Food Drug Adm., Bethesda, MD, 20892, USA
SOURCE: Journal of Immunology (1993), 150(5), 1944-50
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The interaction of interferon (IFN)-α and IFN-γ with monocytes results in several actions that influence the course of an immune response. Many of these effects are proinflammatory and can contribute to the degree of tissue injury at a site of inflammation. Whereas recent investigations target interleukin (IL)-4 as a T cell product that can antagonize some of the responses induced by IFN, little is known regarding the mechanisms involved. Here, taking advantage of two well defined systems, the transcriptional activation of the cellular genes ISG-54 by IFN-α and IP-10 by IFN-γ were examined IL-4 treatment of both the monocytic leukemia cell line, THP-1, and normal peripheral blood monocytes resulted in inhibition of IFN-induced RNA levels for both genes. Nuclear run-on assays in THP-1 cells indicated that the effects of IL-4 were due to the inhibition of the transcriptional activation of these genes by both IFN-α and INF-γ. This inhibition was not due to alteration in the binding characteristics of IFN-α or IFN-γ to the cell. In the IFN-α system, IL-4 treatment resulted in reduced formation of the transcriptional activator, IFN-stimulated gene factor 3. This reduction appears to be the result of a defect in the ability of IFNα to activate the IFN-stimulated gene factor 3α component of IFN-stimulated gene factor 3.

L8 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1983:70164 CAPLUS
DOCUMENT NUMBER: 98:70164
TITLE: Accumulation and breakdown of RNA-deficient intracellular virus particles in interferon-treated NIH 3T3 cells chronically producing Moloney murine leukemia virus
AUTHOR(S): Aboud, Mordechai; Hassan, Yehudith
CORPORATE SOURCE: Fac. Health Sci., Ben Gurion Univ., Beer Sheva, Israel
SOURCE: Journal of Virology (1983), 45(2), 489-95
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interferon treatment of NIH 3T3 cells chronically infected with Moloney murine leukemia virus inhibited about 95% of virus release. This inhibition was accompanied by a 2-3-fold accumulation of intracellular virions. However, this accumulation could be demonstrated only by exogenous reverse transcriptase reaction assay or radioactive labeling of the assembled viral proteins. It could not be shown by the endogenous reverse transcriptase reaction assay, which depends on endogenous viral RNA, or by labeling the encapsidated viral RNA. It was, therefore, evident that most of the intracellular virions accumulated in interferon-treated cells were RNA deficient. Hybridization anal. revealed that these virions were deficient in genomic viral RNA, whereas size anal. by gel electrophoresis suggested that the deficiency of 4 S RNA normally packaged in Moloney murine leukemia virus was even stronger. These data also suggested that this RNA deficiency was not due to a degradation of the encapsidated RNA, but more likely to a defect in virus assembly. RNA-lacking intracellular virions were unstable; they collapsed before being released.

L8 ANSWER 7 OF 15 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:180727 BIOSIS
DOCUMENT NUMBER: PREV200600182839
TITLE: Bone marrow connexin-43 expression is critical for hematopoietic regeneration after chemotherapy.
AUTHOR(S): Lee, Andrew W. [Reprint Author]; Presley, Cynthia A.; Kastl, Bryan D.; Igbinosa, Irogue I.; Yamada, Yoshiyuki; Fishman, Glen I.; Gutstein, David E.; Cancelas, Jose A.
CORPORATE SOURCE: Cincinnati Childrens Hosp, Med Ctr, Div Exp Hematol, Cincinnati, OH USA
SOURCE: Blood, (NOV 16 2005) Vol. 106, No. 11, Part 1, pp. 141A. Meeting Info.: 47th Annual Meeting of the American-Society-of-Hematology. Atlanta, GA, USA. December 10 -13, 2005. Amer Soc Hematol. CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting) Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Mar 2006 Last Updated on STN: 15 Mar 2006

AB Contact between bone marrow (BM) hematopoietic stem cells (HSC) and osteoblast/stromal (OS) cells has been shown to be crucial in the regulation of hematopoiesis. However, very little is known about the regulatory mechanisms of direct cell-to-cell communication in the hematopoietic microenvironment. Gap junctions (GJs) represent the best described intercellular communication (IC) system, and they are characterized by the existence of plaques of narrow channels between contacting cells. Each cell contributes with one hemichannel, which is composed of six proteins, called connexins. Connexin 43 (Cx43) is expressed by BM OS cells. Cx43 has been associated with the cadherin/beta-catenin signaling pathway, recently reported as relevant in the OS/HSC interaction at the stem cell niche. Multiple osteogenic defects have been reported in human Cx43 mutations and Cx43 has been shown to be essential in controlling osteublast functions. BM Cx43 expression is upregulated up to 100-fold by 5-fluorouracil (5-FU) treatment. Due to the perinatal death of Cx43 germline null mice, a conditional genetic approach was employed to study the role of Cx43 in stem cell proliferation and differentiation. The interferon -inducible Mx1 gene is expressed by both hematopoietic and stromal BM cells. Therefore, we crossed Cx43(flox/+) mice with Mx1-Cre transgenic (Mx1-Cre(Tg/-)) mice. Cx43(+/+):Mx1-Cre(Tg/-) and Cx43(flox/flox) Mx1-Cre(Tg/-) littermates have been analyzed. Gene deletion was induced in vivo by injecting the interferon-inducer polyI:C (8 injections of 300 mu g every other day), generating control (Cx43(+)) and Cx43-deficient (Cx43KO) mice. After one week, Cx43+ and Cx43KO mice were injected with 5-FU (150 mg/Kg i.v.). Cx43 expression in Cx43KO BM was

markedly reduced (> 80%) as analyzed on day +14 post-5-FU treatment. Cx43 deficiency did not induce a significant change in peripheral blood counts before 5-FU treatment, but the hematopoiesis recovery after 5-FU treatment was severely impaired as demonstrated by absence of recovery of peripheral blood counts, including profound neutropenia, anemia with reticulocytopenia, thrombocytopenia and a 5 to 8-fold decrease of cellularity and hematopoietic progenitor content (granulomacrophagic colony-forming-units -CFU-GM-, erythroid burst forming units (BFU-E) and mixed colony forming units -CFU-mix-) in BM and spleen on day +14 post-5-FU treatment. However, the femoral content of Lin(-)/c-kit(+)/Scal(+) cells in Cx43KO BM was maintained when compared to Cx43(+) BM (139 +/- 19 vs 117 +/- 32 x 10(3) Lin(-)/c-kit(+)/Scal(+) cells per femur, respectively). Short-term competitive repopulation ability of Cx43KO BM cells was diminished as compared to Cx43+ mice (5.9 +/- 0.35% vs 22.2 +/- 4.6%, respectively, $p < 0.01$), specifically for myeloid (9.2 +/- 1.4% vs 35.8 +/- 4.3%, respectively, $p < 0.001$) and B lymphoid (0.4 +/- 0.2% vs 3.0 +/- 1.0%, respectively, $p < 0.01$) cells, but showed spared long-term (6-month) competitive repopulation ability with roughly normal hematopoietic differentiation. Altogether, these data suggest that hematopoietic regeneration after cycle-specific chemotherapy is blocked in Cx43-deficient mice at the long-term HSC repopulating level. Cx43 expression within the BM appears to be crucial in the development of an efficient response to hematopoietic stress.

L8 ANSWER 8 OF 15 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:139976 BIOSIS
DOCUMENT NUMBER: PREV200400133496
TITLE: Depletion and dysfunction of blood plasmacytoid dendritic cells in human T-cell lymphotropic virus type-I-infected individuals.
AUTHOR(S): Hishizawa, Masakatsu [Reprint Author]; Imada, Kazunori [Reprint Author]; Kitawaki, Toshio [Reprint Author]; Kadowaki, Norimitsu [Reprint Author]; Uchiyama, Takashi [Reprint Author]
CORPORATE SOURCE: Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 278a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 2004
Last Updated on STN: 10 Mar 2004

AB Adult T-cell leukemia (ATL) is caused by human T-cell lymphotropic virus type I (HTLV-I). It is known that opportunistic infections are frequently observed in ATL patients. However, the underlying mechanisms of such immunodeficiency remain obscure. Dendritic cells (DCs) are able to initiate immune response. In human peripheral blood, there are two main subsets of DCs on the basis of differences in phenotype and function; lineage marker (Lin)-/CD11c+/CD4+ myeloid DCs (myDCs) and Lin-/CD11c-CD123+/CD4+ plasmacytoid DCs (pcDCs). In response to viruses and other pathogens, pcDCs produce enormous amount of type I interferons (IN) and thereafter differentiate into mature DCs. myDCs are precursors of Langerhans cells and dermal and intestinal DCs. Therefore, DC defects in HTLV-I infection would decrease innate and adaptive immune responses against opportunistic pathogens and the virus. In this study, we analyzed the absolute numbers of these two DC subsets using 3-color flow

cytometry in 17 uninfected healthy controls and 22 HTLV-I-infected individuals. ATL patients had a significant decrease in the numbers of pcDCs (median 1.32/mul; range 0-15.30) and myDCs (median 5.61/mul; range 0-42.84) compared with controls (pcDC: median 4.09/mul; range 1.19-29.75; p<0.05; myDCs: median 14.89/mul; range 3.19-90.5; p<0.05). IFN-alpha producing capacity of PBMCs in response to HSV-I was markedly reduced in ATL patients (median 120pg/ml; range 0-1052) compared with controls (median 1677pg/ml; range 380-17000, p<0.01). Purified pcDCs from an ATL patient was severely impaired in the capacity of IFN-alpha production (4128pg/ml) compared with controls (median 46150pg/ml; range 28576-214789). These results indicate that depletion and dysfunction of pcDCs along with depletion of myDCs may contribute to the immunodeficiency observed in patients with ATL. On the other hand, the numbers of both pcDCs and myDCs in HTLV-I infected asymptomatic carriers (ACs) (pcDC: median 5.46/mul; range 1.75-12.90; myDC: median 20.83/mul; range 4.37-57.08) were comparable to those noted in controls. The capacity of IFN-alpha production by PBMCs was not significantly impaired in ACs (median 1118pg/ml; range 0-3362), but the isolated pcDCs had a tendency to decrease in IFN-alpha production (median 10187pg/ml; range 3334-53900) compared with controls. Interestingly, an inverse correlation was found between IFN-alpha producing capacity and HTLV-I proviral load in PBMCs from ACs (rs-0.48, p<0.05), suggesting that pcDCs may play an important role in controlling HTLV-I infection and maintaining the carrier state. Taken together, these data provide the first evidence that depletion and dysfunction of blood DCs may contribute to the immunodeficiency in ATL patients as well as the development of ATL.

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=> D history

     (FILE 'HOME' ENTERED AT 10:48:38 ON 25 OCT 2006)

     FILE 'CAPLUS, BIOSIS' ENTERED AT 10:49:06 ON 25 OCT 2006
L1         57295 INTERFERON (P) RESPONSE
L2       9442219 3
L3         15930 L1 AND L2
L4           265 DEFECT AND L3
L5          1339 CANCER AND L3
L6            19 NEOPLASM AND L4
L7            77 TUMOR  AND L4
L8            15 LEUKEMIA AND L4

=> VSV and L7
L9             4 VSV AND L7

=> VSV and L6
L10            2 VSV AND L6

=> D L10 IBIB ABS 1-2

L10  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:57860  CAPLUS
DOCUMENT NUMBER:          138:117637
TITLE:                    Recombinant vesicular stomatitis virus (VSV)
                          vector for the treatment of tumor cells
INVENTOR(S):              Barber, Glen
PATENT ASSIGNEE(S):       University of Miami, USA
SOURCE:                   PCT Int. Appl., 85 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003005964	A2	20030123	WO 2002-US22146	20020711
WO 2003005964	A3	20030424		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2452517	AA	20030123	CA 2002-2452517	20020711
US 2003044386	A1	20030306	US 2002-194594	20020711
EP 1411880	A2	20040428	EP 2002-749985	20020711
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2004537305	T2	20041216	JP 2003-511773	20020711
PRIORITY APPLN. INFO.:			US 2001-304125P P	20010711
			WO 2002-US22146 W	20020711

AB The invention provides compns. and methods for the treatment of tumor and/or malignant and/or cancerous cells. The invention provides VSV vectors comprising nucleic acid encoding a cytokine, e..g interleukin or interferon, or a suicide gene, e.g. thymidine kinase, or other biol. protein, e.g. heat shock protein gp96, or endostatin or angiostatin, wherein the VSV vectors exhibit greater oncolytic activity against the tumor and/or malignant and/or cancerous cell than a wild-type VSV vector. The invention also provides methods of making such vectors, host cells, expression systems, and compns. comprising the VSV vectors, and viral particles comprising the VSV vectors. The invention further provides methods for producing oncolytic activity in a tumor and/or malignant and/or cancerous cell comprising contacting the cell with a VSV vector of the invention. The invention also provides methods for suppressing tumor growth comprising contacting the tumor with a VSV vector of the invention. The invention further provides methods for eliciting an immune response to a tumor cell in an individual.

L10 ANSWER 2 OF 2 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:82408 BIOSIS

DOCUMENT NUMBER: PREV200500076460

TITLE: Sensitivity of prostate tumors to wild type and M protein mutant vesicular stomatitis viruses.

AUTHOR(S): Ahmed, Maryam [Reprint Author]; Cramer, Scott D.; Lyles, Douglas S.

CORPORATE SOURCE: Sch MedDept Biochem, Wake Forest Univ, Med Ctr Blvd, Winston Salem, NC, 27157, USA
mahmed@wfubmc.edu

SOURCE: Virology, (December 5 2004) Vol. 330, No. 1, pp. 34-49. print.
ISSN: 0042-6822 (ISSN print).

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 23 Feb 2005
Last Updated on STN: 23 Feb 2005

AB Because of its potent ability to induce apoptosis, vesicular stomatitis virus (VSV) is an attractive candidate as an oncolytic virus for tumor therapy. Previous studies have suggested that VSV selectively infects tumor cells due to defects in their antiviral responses making them more susceptible to VSV infection than normal cells. We tested this hypothesis in the prostate

tumor system by comparing LNCaP and PC-3 prostate tumor cells to benign human prostatic epithelial cells from patient prostatectomy specimens. We compared the cell killing ability of a recombinant virus containing a wild-type (wt) M protein (rwt) and an isogenic M protein mutant virus (rM51R-M) that induces interferon (IFN) in infected cells and should display a greater selectivity for tumor cells. Our results showed that in single-cycle infection experiments, LNCaP cells were sensitive to killing by both wt and mutant viruses, while PC-3 cells were highly resistant to VSV-induced cell killing. LNCaP and benign prostate cells were similarly susceptible to both viruses, indicating that normal prostate cells are not inherently resistant to killing by VSV. In each of the cell lines, the rM51R-M virus induced similar levels of apoptosis to rwt virus, showing that the M protein does not play a significant role in apoptosis induction by VSV in these cells. In multiple-cycle infection experiments, LNCaP cells were more sensitive than benign prostatic epithelial cells to virus-induced cell killing by rM51R-M virus, but not rwt virus. Both viruses were equally effective at reducing LNCaP tumor volume in vivo following intratumoral and intravenous inoculation in nude mice, while PC-3 tumors were resistant to VSV treatment. None of the mice treated with rM51R-M virus died as a result of virus infection, while 50-71% of mice treated with rwt virus succumbed to virus infection. Similarly, when inoculated by the more sensitive intranasal route, the rM51R-M virus was less pathogenic than the rwt virus from which it was derived. These results indicate that M protein mutant viruses are superior candidates as oncolytic viruses for therapies of prostate tumors, but future strategies for use of VSV will require testing individual tumors for their susceptibility to virus infection.

=> D L9 IBIB ABS 1-4

L9 ANSWER 1 OF 4 CAPLUS
ACCESSION NUMBER: 2004:953474 CAPLUS
TITLE: Sensitivity of prostate tumors to wild type and M protein mutant vesicular stomatitis viruses
AUTHOR(S): Ahmed, Maryam; Cramer, Scott D.; Lyles, Douglas S.
CORPORATE SOURCE: Department of Biochemistry, Wake Forest University School of Medicine, Winston-Salem, NC, 27157, USA
SOURCE: Virology (2004), 330(1), 34-49
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Because of its potent ability to induce apoptosis, vesicular stomatitis virus (VSV) is an attractive candidate as an oncolytic virus for tumor therapy. Previous studies have suggested that VSV selectively infects tumor cells due to defects in their antiviral responses making them more susceptible to VSV infection than normal cells. We tested this hypothesis in the prostate tumor system by comparing LNCaP and PC-3 prostate tumor cells to benign human prostatic epithelial cells from patient prostatectomy specimens. We compared the cell killing ability of a recombinant virus containing a wild-type (wt) M protein (rwt) and an isogenic M protein mutant virus (rM51R-M) that induces interferon (IFN) in infected cells and should display a greater selectivity for tumor cells. Our results showed that in single-cycle infection expts., LNCaP cells were sensitive to killing by both wt and mutant viruses, while PC-3 cells were highly resistant to VSV-induced cell killing. LNCaP and benign prostate cells were similarly susceptible to both viruses, indicating that normal prostate cells are not inherently resistant to killing by VSV. In each of the cell lines, the rM51R-M virus induced similar

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REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:57860 CAPLUS
DOCUMENT NUMBER: 138:117637
TITLE: Recombinant vesicular stomatitis virus (VSV) vector for the treatment of tumor cells
INVENTOR(S): Barber, Glen
PATENT ASSIGNEE(S): University of Miami, USA
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003005964	A2	20030123	WO 2002-US22146	20020711
WO 2003005964	A3	20030424		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2452517	AA	20030123	CA 2002-2452517	20020711
US 2003044386	A1	20030306	US 2002-194594	20020711
EP 1411880	A2	20040428	EP 2002-749985	20020711
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2004537305	T2	20041216	JP 2003-511773	20020711

PRIORITY APPLN. INFO.:
US 2001-304125P P 20010711
WO 2002-US22146 W 20020711

AB The invention provides compns. and methods for the treatment of tumor and/or malignant and/or cancerous cells. The invention provides VSV vectors comprising nucleic acid encoding a cytokine, e..g interleukin or interferon, or a suicide gene, e.g. thymidine kinase, or other biol. protein, e.g. heat shock protein gp96, or endostatin or angiostatin, wherein the VSV vectors exhibit greater oncolytic activity against the tumor and/or malignant and/or cancerous cell than a wild-type VSV vector. The invention also provides methods of making such vectors, host cells,

expression systems, and compns. comprising the VSV vectors, and viral particles comprising the VSV vectors. The invention further provides methods for producing oncolytic activity in a tumor and/or malignant and/or cancerous cell comprising contacting the cell with a VSV vector of the invention. The invention also provides methods for suppressing tumor growth comprising contacting the tumor with a VSV vector of the invention. The invention further provides methods for eliciting an immune response to a tumor cell in an individual.

L9 ANSWER 3 OF 4 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:82408 BIOSIS
DOCUMENT NUMBER: PREV200500076460
TITLE: Sensitivity of prostate tumors to wild type and M protein mutant vesicular stomatitis viruses.
AUTHOR(S): Ahmed, Maryam [Reprint Author]; Cramer, Scott D.; Lyles, Douglas S.
CORPORATE SOURCE: Sch MedDept Biochem, Wake Forest Univ, Med Ctr Blvd, Winston Salem, NC, 27157, USA
mahmed@wfubmc.edu
SOURCE: Virology, (December 5 2004) Vol. 330, No. 1, pp. 34-49. print.
ISSN: 0042-6822 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Feb 2005
Last Updated on STN: 23 Feb 2005

AB Because of its potent ability to induce apoptosis, vesicular stomatitis virus (VSV) is an attractive candidate as an oncolytic virus for tumor therapy. Previous studies have suggested that VSV selectively infects tumor cells due to defects in their antiviral responses making them more susceptible to VSV infection than normal cells. We tested this hypothesis in the prostate tumor system by comparing LNCaP and PC-3 prostate tumor cells to benign human prostatic epithelial cells from patient prostatectomy specimens. We compared the cell killing ability of a recombinant virus containing a wild-type (wt) M protein (rwt) and an isogenic M protein mutant virus (rM51R-M) that induces interferon (IFN) in infected cells and should display a greater selectivity for tumor cells. Our results showed that in single-cycle infection experiments, LNCaP cells were sensitive to killing by both wt and mutant viruses, while PC-3 cells were highly resistant to VSV-induced cell killing. LNCaP and benign prostate cells were similarly susceptible to both viruses, indicating that normal prostate cells are not inherently resistant to killing by VSV. In each of the cell lines, the rM51R-M virus induced similar levels of apoptosis to rwt virus, showing that the M protein does not play a significant role in apoptosis induction by VSV in these cells. In multiple-cycle infection experiments, LNCaP cells were more sensitive than benign prostatic epithelial cells to virus-induced cell killing by rM51R-M virus, but not rwt virus. Both viruses were equally effective at reducing LNCaP tumor volume in vivo following intratumoral and intravenous inoculation in nude mice, while PC-3 tumors were resistant to VSV treatment. None of the mice treated with rM51R-M virus died as a result of virus infection, while 50-71% of mice treated with rwt virus succumbed to virus infection. Similarly, when inoculated by the more sensitive intranasal route, the rM51R-M virus was less pathogenic than the rwt virus from which it was derived. These results indicate that M protein mutant viruses are superior candidates as oncolytic viruses for therapies of prostate tumors, but future strategies for use of VSV will require testing individual tumors for their susceptibility to virus infection.

L9 ANSWER 4 OF 4 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:394567 BIOSIS
DOCUMENT NUMBER: PREV200000394567
TITLE: An indoleamine 2,3-dioxygenase-negative mutant is defective in Stat1 DNA binding: Differential response to IFN-gamma and IFN-alpha.
AUTHOR(S): Sotero-Esteva, Walter D.; Wolfe, Darin; Ferris, Mary; Taylor, Milton W. [Reprint author]
CORPORATE SOURCE: Department of Biology, Indiana University, 1001 East 3rd Street, Jordan Hall 343, Bloomington, IN, 47405, USA
SOURCE: Journal of Interferon and Cytokine Research, (July, 2000) Vol. 20, No. 7, pp. 623-632. print.
ISSN: 1079-9907.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Sep 2000
Last Updated on STN: 8 Jan 2002

AB We have previously reported the isolation of mutant cell lines from the human carcinoma line ME180 that are resistant to the antiproliferative effect of interferon-gamma (IFN-gamma). These cell lines were defective in the induction of indoleamine 2,3-dioxygenase (IDO), a key enzyme of tryptophan catabolism. One of these cell lines, 3B6A, was chosen for further study. This cell line was also defective in the ability of IFN-gamma to protect against vesicular stomatitis virus (VSV) infection. However it maintained a normal antiviral response to IFN-alpha. A promoter-chloramphenicol acetyltransferase (CAT) construct containing the promoter region of IDO, which includes IFN-gamma activation site (GAS), IFN-stimulated response element-1 (ISRE-1), and ISRE-2 regions, was not expressed in 3B6A in the presence of IFN-gamma, indicating that the defect was likely to be in either Stat1 or IFN regulatory factor-1 (IRF-1), transcription factors known to bind to these cis-acting sequences. The induction of other IFN-gamma-inducible genes, such as tryptophanyl-tRNA synthetase (hWRS), was also affected. Electrophoretic mobility shift assays (EMSA) comparing nuclear extracts from parental and mutant cells indicated that Stat1 from the mutant did not bind to GAS sequences. However, Western blot analysis indicated that Stat1 protein was present. This IDO-negative phenotype can be reversed by transfection with a Stat1 expression vector. DNA sequencing of the Stat1 cDNA from wild-type and 3B6A cells indicated that an amino acid change occurred in the Stat1 protein of the mutant at W573, a tryptophan conserved in all known Stat proteins. We hypothesize that a change in this region of the Stat protein affects the response to IFN-gamma but not to IFN-alpha.

=> oncolytic and l4
L11 3 ONCOLYTIC AND L4

=> D L11 IBIB ABs 1-3

L11 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:953474 CAPLUS
TITLE: Sensitivity of prostate tumors to wild type and M protein mutant vesicular stomatitis viruses
AUTHOR(S): Ahmed, Maryam; Cramer, Scott D.; Lyles, Douglas S.
CORPORATE SOURCE: Department of Biochemistry, Wake Forest University School of Medicine, Winston-Salem, NC, 27157, USA
SOURCE: Virology (2004), 330(1), 34-49
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Because of its potent ability to induce apoptosis, vesicular stomatitis virus (VSV) is an attractive candidate as an oncolytic virus for

tumor therapy. Previous studies have suggested that VSV selectively infects tumor cells due to defects in their antiviral responses making them more susceptible to VSV infection than normal cells. We tested this hypothesis in the prostate tumor system by comparing LNCaP and PC-3 prostate tumor cells to benign human prostatic epithelial cells from patient prostatectomy specimens. We compared the cell killing ability of a recombinant virus containing a wild-type (wt) M protein (rwt) and an isogenic M protein mutant virus (rM51R-M) that induces interferon (IFN) in infected cells and should display a greater selectivity for tumor cells. Our results showed that in single-cycle infection expts., LNCaP cells were sensitive to killing by both wt and mutant viruses, while PC-3 cells were highly resistant to VSV-induced cell killing. LNCaP and benign prostate cells were similarly susceptible to both viruses, indicating that normal prostate cells are not inherently resistant to killing by VSV. In each of the cell lines, the rM51R-M virus induced similar levels of apoptosis to rwt virus, showing that the M protein does not play a significant role in apoptosis induction by VSV in these cells. In multiple-cycle infection expts., LNCaP cells were more sensitive than benign prostatic epithelial cells to virus-induced cell killing by rM51R-M virus, but not rwt virus. Both viruses were equally effective at reducing LNCaP tumor volume in vivo following intratumoral and i.v. inoculation in nude mice, while PC-3 tumors were resistant to VSV treatment. None of the mice treated with rM51R-M virus died as a result of virus infection, while 50-71% of mice treated with rwt virus succumbed to virus infection. Similarly, when inoculated by the more sensitive intranasal route, the rM51R-M virus was less pathogenic than the rwt virus from which it was derived. These results indicate that M protein mutant viruses are superior candidates as oncolytic viruses for therapies of prostate tumors, but future strategies for use of VSV will require testing individual tumors for their susceptibility to virus infection.

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L11 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:57860 CAPLUS
DOCUMENT NUMBER: 138:117637
TITLE: Recombinant vesicular stomatitis virus (VSV) vector for the treatment of tumor cells
INVENTOR(S): Barber, Glen
PATENT ASSIGNEE(S): University of Miami, USA
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003005964	A2	20030123	WO 2002-US22146	20020711
WO 2003005964	A3	20030424		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2452517	AA	20030123	CA 2002-2452517	20020711
US 2003044386	A1	20030306	US 2002-194594	20020711

EP 1411880 A2 20040428 EP 2002-749985 20020711
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY; AL, TR, BG, CZ, EE, SK
JP 2004537305 T2 20041216 JP 2003-511773 20020711
PRIORITY APPLN. INFO.: US 2001-304125P P 20010711
WO 2002-US22146 W 20020711

AB The invention provides compns. and methods for the treatment of tumor and/or malignant and/or cancerous cells. The invention provides VSV vectors comprising nucleic acid encoding a cytokine, e..g interleukin or interferon, or a suicide gene, e.g. thymidine kinase, or other biol. protein, e.g. heat shock protein gp96, or endostatin or angiostatin, wherein the VSV vectors exhibit greater oncolytic activity against the tumor and/or malignant and/or cancerous cell than a wild-type VSV vector. The invention also provides methods of making such vectors, host cells, expression systems, and compns. comprising the VSV vectors, and viral particles comprising the VSV vectors. The invention further provides methods for producing oncolytic activity in a tumor and/or malignant and/or cancerous cell comprising contacting the cell with a VSV vector of the invention. The invention also provides methods for suppressing tumor growth comprising contacting the tumor with a VSV vector of the invention. The invention further provides methods for eliciting an immune response to a tumor cell in an individual.

L11 ANSWER 3 OF 3 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:82408 BIOSIS
DOCUMENT NUMBER: PREV200500076460
TITLE: Sensitivity of prostate tumors to wild type and M protein mutant vesicular stomatitis viruses.
AUTHOR(S): Ahmed, Maryam [Reprint Author]; Cramer, Scott D.; Lyles, Douglas S.
CORPORATE SOURCE: Sch MedDept Biochem, Wake Forest Univ, Med Ctr Blvd, Winston Salem, NC, 27157, USA
mahmed@wfubmc.edu
SOURCE: Virology, (December 5 2004) Vol. 330, No. 1, pp. 34-49. print.
ISSN: 0042-6822 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Feb 2005
Last Updated on STN: 23 Feb 2005

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=> D history

     (FILE 'HOME' ENTERED AT 10:48:38 ON 25 OCT 2006)

     FILE 'CAPLUS, BIOSIS' ENTERED AT 10:49:06 ON 25 OCT 2006
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L2       9442219 3
L3         15930 L1 AND L2
L4           265 DEFECT AND L3
L5          1339 CANCER AND L3
L6            19 NEOPLASM AND L4
L7            77 TUMOR  AND L4
L8            15 LEUKEMIA AND L4
L9             4 VSV AND L7
L10            2 VSV AND L6
L11            3 ONCOLYTIC AND L4

=> oncolytic and l1
L12           52 ONCOLYTIC AND L1

=> VSV and L12
L13           18 VSV AND L12

=> D L13 IBIB ABS 1-18

L13  ANSWER 1 OF 18  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2006:198241  CAPLUS
DOCUMENT NUMBER:          144:346651
TITLE:                    Matrix protein mutant of vesicular stomatitis virus
                          stimulates maturation of myeloid dendritic cells
AUTHOR(S):                Ahmed, Maryam; Brzoza, Kristina L.; Hiltbold,
                          Elizabeth M.
CORPORATE SOURCE:         Department of Biochemistry, Wake Forest University
                          School of Medicine, Winston-Salem, NC, 27157, USA
SOURCE:                   Journal of Virology (2006), 80(5), 2194-2205
                          CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER:                American Society for Microbiology
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Matrix (M) protein mutants of vesicular stomatitis virus have recently
     been used as oncolytic viruses for tumor therapies and are being
     developed as vaccine vectors for heterologous antigens. Because dendritic
     cell (DC) maturation is an important correlate of tumor immunosurveillance
     and vaccine efficacy, we sought to determine the ability of a recombinant M
     protein mutant virus (rM51R-M virus) to mature DC in vitro. We have
     previously shown that rM51R-M virus is defective at inhibiting host gene
     expression in several cell lines compared to its recombinant wild-type
     counterpart, rwt virus. Therefore, rM51R-M virus allows the expression of
     genes involved in antiviral responses, such as the type I
     interferon (IFN) gene. Our results demonstrate that, in contrast
     to the rwt virus, rM51R-M virus induced the maturation of myeloid DC (mDC)
     populations, as indicated by an increase in the surface expression of
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CD40, CD80, and CD86 as well as the secretion of interleukin-12 (IL-12), IL-6, and type I IFN. In addition, mDC infected with rM51R-M virus effectively activated naive T cells in vitro, whereas rwt virus-infected mDC were defective in antigen presentation. The inability of rwt virus to induce mDC maturation was correlated with the inhibition of host gene expression in rwt virus-infected cells. Our studies also indicated that the production of costimulatory mols. on mDC by rM51R-M virus was dependent on the type I IFN receptor, while maturation induced by this virus was largely independent of MyD88. These data indicate that rM51R-M virus effectively stimulates the maturation of mDC and has the potential to promote effective T-cell responses to vector-expressed antigens, activate DC at tumor sites during therapy, and aid in tumor immunosurveillance and destruction.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1229042 CAPLUS
DOCUMENT NUMBER: 144:49701
TITLE: VSV-tumor selective replication and protein translation
AUTHOR(S): Barber, Glen N.
CORPORATE SOURCE: Department of Microbiology and Immunology, Sylvester Comprehensive Cancer Center, University of Miami School of Medicine, Miami, FL, 33136, USA
SOURCE: Oncogene (2005), 24(52), 7710-7719
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The emergence of vesicular stomatitis virus (VSV) as a potent antitumor agent has made a dissection of the mol. determinants of host-cell permissiveness to this virus an important objective. Such insight would not only enable the intelligent design of future generations of recombinant VSV vectors to combat disease, but may also resolve general features of cellular transformation that may be exploited by this virus, and perhaps other oncolytic viruses. The defective pathways underlining the oncolytic activity of VSV remain to be fully determined but recent data indicates that flaws in innate immune responses, involving the interferon (IFN) system, may commonly occur in tumor cells and thus play a large role in facilitating oncolysis. Aside from the IFN system, however, it is almost certain that other key cellular pathways may be similarly defective and therefore cooperatively contribute towards mediating rapid oncolytic virus activity. Recent data have indicated that defects in cancer cell translational regulation could be one area that may be exploited by VSV. Certainly, all viruses require cellular protein synthesis pathways to facilitate their replication and many have devised numerous mechanisms to ensure that viral mRNAs become translated at the expense of the host. Using VSV as a model, this review will discuss some of the recent developments in the fields of innate immunity and translational regulation that may help explain mechanisms of viral oncolysis.

REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1170417 CAPLUS
DOCUMENT NUMBER: 143:420671
TITLE: Prophylactic alpha interferon treatment increases the therapeutic index of oncolytic vesicular stomatitis virus virotherapy for advanced hepatocellular carcinoma in immune-competent rats
AUTHOR(S): Shinozaki, Katsunori; Ebert, Oliver; Suriawinata,

Arief; Thung, Swan N.; Woo, Savio L. C.
CORPORATE SOURCE: Department of Gene and Cell Medicine, Mount Sinai School of Medicine, New York, NY, 10029-6574, USA
SOURCE: Journal of Virology (2005), 79(21), 13705-13713
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Vesicular stomatitis virus (VSV) is a neg.-strand RNA virus with intrinsic oncolytic specificity due to substantially attenuated antiviral responses in many tumors. The authors have recently reported that recombinant VSV vector can be used as an effective oncolytic agent to safely treat multifocal hepatocellular carcinoma (HCC) in the livers of immune-competent rats via hepatic artery infusion. When administered at doses above the maximum tolerated dose (MTD), however, the animals suffered from neurotoxicity and/or acute lethal hepatotoxicity. Since VSV is extremely sensitive to the antiviral actions of alpha/beta interferon (IFN-α/β) in normal cells, the authors tested if prophylactic treatment with rat IFN-α would enhance VSV safety without compromising treatment efficacy in tumor-bearing rats. The authors found that VSV retained its replication potential in human and rat HCC cells after preincubation with relatively high doses of rat and human IFN-α in vitro, and its MTD in tumor-bearing rats treated systemically with rat IFN-α at 66 IU/g body weight (BW), equivalent to a human IFN-α dose that is currently prescribed for patients with viral hepatitis, was elevated by more than 1/2 log unit. Furthermore, the authors demonstrate that intratumoral replication of VSV was not attenuated by administration of 66 IU/g BW rat IFN-α, as tumor response and survival advantage in VSV-treated rats in the presence or absence of rat IFN-α were equivalent The results suggest that prophylactic rat IFN-α treatment elevates the therapeutic index of hepatic arterial VSV therapy for multifocal HCC in rats. Since human IFN-α is currently in clin. use, its prophylactic application should be considered in future clin. translational protocols for VSV-mediated oncolytic virotherapy as a novel therapeutic modality in patients with advanced HCC, as well as other types of cancer.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1038076 CAPLUS
DOCUMENT NUMBER: 144:80330
TITLE: Vesicular stomatitis: an oncolytic virus that exploits tumor-specific defects in the interferon pathway
AUTHOR(S): Taylor, Rebecca Ann C.; Paterson, Jennifer M.; Bell, John C.
CORPORATE SOURCE: Research Laboratories, Ottawa Regional Cancer Centre, Ottawa, ON, Can.
SOURCE: Viral Therapy of Human Cancers (2005), 597-625.
Editor(s): Sinkovics, Joseph G.; Horvath, Joseph C.
Marcel Dekker, Inc.: New York, N. Y.
CODEN: 69HIM6; ISBN: 0-8247-5913-3
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review. Vesicular stomatitis virus (VSV) is part of a new generation of small RNA viruses being developed as replicating cancer therapeutics. Vesicular stomatitis virus replicates in and kills a wide variety of human cancer cell lines, and is highly effective in mouse cancer models. It is exquisitely sensitive to the antiviral effects of the interferon (IFN) family of cytokines and its oncolytic activity depends on the presence of inherent defects in

the IFN signaling pathway in cancer cells. Recent research has shown that IFN-inducing VSV mutants are attenuated in normal cells, but not in cancer cells. These mutants can be administered i.v. to mice at high doses, and can effect durable cures in disseminated cancer models. Other research has highlighted the potential of VSV engineered to express transgenes that could enhance the antitumor immune response, cause bystander-cell killing, or retarget VSV to receptors expressed at high levels on cancer cells. Now that several first-generation oncolytic viruses have entered into clin. trials, the lessons learned from these viruses can be applied to second-generation viruses, such as VSV, to develop more effective, safe, replicating cancer therapeutics.

REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:25741 CAPLUS
DOCUMENT NUMBER: 142:132506
TITLE: Vesicular stomatitis virus as an oncolytic vector
AUTHOR(S): Barber, Glen N.
CORPORATE SOURCE: Department of Microbiology and Immunology, Sylvester Comprehensive Cancer Center, University of Miami School of Medicine, Miami, FL, USA
SOURCE: Viral Immunology (2004), 17(4), 516-527
CODEN: VIIMET; ISSN: 0882-8245
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Recent data has shown that viruses such as vesicular stomatitis virus (VSV), a relatively non-pathogenic, neg.-stranded RNA virus, can preferentially replicate in malignant cells and less so in normal cells. VSV appears able to carry out this function in transformed cells since these hosts exhibit the hallmarks of flawed host defense, probably involving the interferon system, which is essential for preventing virus replication. The simple genetic constitution of VSV, lack of any known transforming, integrating or reassortment properties, extensive knowledge relating to its interaction with the immune system and the ability to genetically manipulate this agent affords an ideal opportunity to exploit the oncolytic and gene targeting potential of this innocuous virus. Thus, aside from preferentially targeting malignant cells VSV recombinants could be generated that could increase a tumor's susceptibility to chemotherapeutic agents and/ or importantly, the host immune response. Collectively, our data and others demonstrate that VSV as well as other RNA viruses could provide a promising and exciting approach to cancer therapy.

REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:953474 CAPLUS
TITLE: Sensitivity of prostate tumors to wild type and M protein mutant vesicular stomatitis viruses
AUTHOR(S): Ahmed, Maryam; Cramer, Scott D.; Lyles, Douglas S.
CORPORATE SOURCE: Department of Biochemistry, Wake Forest University School of Medicine, Winston-Salem, NC, 27157, USA
SOURCE: Virology (2004), 330(1), 34-49
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Because of its potent ability to induce apoptosis, vesicular stomatitis virus (VSV) is an attractive candidate as an oncolytic

virus for tumor therapy. Previous studies have suggested that VSV selectively infects tumor cells due to defects in their antiviral responses making them more susceptible to VSV infection than normal cells. We tested this hypothesis in the prostate tumor system by comparing LNCaP and PC-3 prostate tumor cells to benign human prostatic epithelial cells from patient prostatectomy specimens. We compared the cell killing ability of a recombinant virus containing a wild-type (wt) M protein (rwt) and an isogenic M protein mutant virus (rM51R-M) that induces interferon (IFN) in infected cells and should display a greater selectivity for tumor cells. Our results showed that in single-cycle infection expts., LNCaP cells were sensitive to killing by both wt and mutant viruses, while PC-3 cells were highly resistant to VSV-induced cell killing. LNCaP and benign prostate cells were similarly susceptible to both viruses, indicating that normal prostate cells are not inherently resistant to killing by VSV. In each of the cell lines, the rM51R-M virus induced similar levels of apoptosis to rwt virus, showing that the M protein does not play a significant role in apoptosis induction by VSV in these cells. In multiple-cycle infection expts., LNCaP cells were more sensitive than benign prostatic epithelial cells to virus-induced cell killing by rM51R-M virus, but not rwt virus. Both viruses were equally effective at reducing LNCaP tumor volume in vivo following intratumoral and i.v. inoculation in nude mice, while PC-3 tumors were resistant to VSV treatment. None of the mice treated with rM51R-M virus died as a result of virus infection, while 50-71% of mice treated with rwt virus succumbed to virus infection. Similarly, when inoculated by the more sensitive intranasal route, the rM51R-M virus was less pathogenic than the rwt virus from which it was derived. These results indicate that M protein mutant viruses are superior candidates as oncolytic viruses for therapies of prostate tumors, but future strategies for use of VSV will require testing individual tumors for their susceptibility to virus infection.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:534872 CAPLUS

DOCUMENT NUMBER: 142:16351

TITLE: Recombinant vesicular stomatitis virus vectors as oncolytic agents in the treatment of high-grade gliomas in an organotypic brain tissue slice-glioma coculture model

AUTHOR(S): Duntsch, Christopher D.; Zhou, Qihong; Jayakar, Himangi R.; Weimar, James D.; Robertson, Jon H.; Pfeffer, Lawrence M.; Wang, Lie; Xiang, Zixiu; Whitt, Michael A.

CORPORATE SOURCE: Departments of Neurosurgery, Pathology and Laboratory Medicine, and Molecular Sciences, The University of Tennessee Health Science Center, Memphis, TN, USA

SOURCE: Journal of Neurosurgery (2004), 100(6), 1049-1059
CODEN: JONSAC; ISSN: 0022-3085

PUBLISHER: American Association of Neurological Surgeons

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Object: The purpose of this study was to evaluate both replication-competent and replication-restricted recombinant vesicular stomatitis virus (VSV) vectors as therapeutic agents for high-grade gliomas by using an organotypic brain tissue slice-glioma coculture system. Methods: The coculture system involved growing different brain structures together to allow neurons from these tissues to develop synaptic connections similar to those found in vivo. Rat C6 or human U87 glioma cells were then introduced into the culture to evaluate VSV as an oncolytic therapy. The authors found that recombinant wild-type VSV (rVSV-wt) rapidly eliminated C6 glioma

cells from the coculture, but also caused significant damage to neurons, as measured by a loss of microtubule-associated protein 2 immunoreactivity and a failure in electrophysiol. responses from neurons in the tissue slice. Nonetheless, pretreatment with interferon beta (IFNβ) virtually eliminated VSV infection in healthy tissues without impeding any oncolytic effects on tumor cells. Despite the protective effects of the IFNβ pretreatment, the tissue slices still showed signs of cytopathol. when exposed to rVSV-weight In contrast, pretreatment with IFNβ and inoculation with a replication-restricted vector with its glycoprotein gene deleted (rVSV-ΔG) effectively destroyed rat C6 and human U87 glioma cells in the coculture, without causing detectable damage to the neuronal integrity and electrophysiol. properties of the healthy tissue in the culture. Conclusions: Data in this study provide in vitro proof-of-principle that rVSV-ΔG is an effective oncolytic agent that has minimal toxic side effects to neurons compared with rVSV-wt and therefore should be considered for development as an adjuvant to surgery in the treatment of glioma.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:620161 CAPLUS

DOCUMENT NUMBER: 139:244498

TITLE: Development of recombinant vesicular stomatitis viruses that exploit defects in host defense to augment specific oncolytic activity

AUTHOR(S): Obuchi, Masatsugu; Fernandez, Marilyn; Barber, Glen N.

CORPORATE SOURCE: Department of Microbiology and Immunology and Sylvester Comprehensive Cancer Center, University of Miami School of Medicine, Miami, FL, 33136, USA

SOURCE: Journal of Virology (2003), 77(16), 8843-8856
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Vesicular stomatitis virus (VSV) is a neg.-stranded RNA virus normally sensitive to the antiviral actions of alpha/beta interferon (IFN-α/β). Recently, the authors reported that VSV replicates to high levels in many transformed cells due, in part, to susceptible cells harboring defects in the IFN system. These observations were exploited to demonstrate that VSV can be used as a viral oncolytic agent to eradicate malignant cells in vivo while leaving normal tissue relatively unaffected. To attempt to improve the specificity and efficacy of this system as a potential tool in gene therapy and against malignant disease, the authors have genetically engineered VSV that expresses the murine IFN-β gene. The resultant virus (VSV-IFNβ) was successfully propagated in cells not receptive to murine IFN-α/β and expressed high levels of functional heterologous IFN-β. In normal murine embryonic fibroblasts (MEFs), the growth of VSV-IFNβ was greatly reduced and diminished cytopathic effect was observed due to the production of recombinant IFN-β, which by functioning in a manner involving autocrine and paracrine mechanisms induced an antiviral effect, preventing virus growth. However, VSV-IFNβ grew to high levels and induced the rapid apoptosis of transformed cells due to defective IFN pathways being prevalent and thus unable to initiate proficient IFN-mediated host defense. Importantly, VSV expressing the human IFN-β gene (VSV-hIFNβ) behaved comparably and, while nonlytic to normal human cells, readily killed their malignant counterparts. Similar to the authors' in vitro observations, following i.v. and intranasal inoculation in mice, recombinant VSV (rVSV)-IFNβ was also significantly attenuated compared to wild-type VSV or rVSV expressing green fluorescent protein. However,

VSV-IFNβ retained propitious oncolytic activity against metastatic lung disease in immunocompetent animals and was able to generate robust antitumor T-cell responses. The authors' data indicate that rVSV designed to exploit defects in mechanisms of host defense can provide the basis for new generations of effective, specific, and safer viral vectors for the treatment of malignant and other disease.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:57860 CAPLUS
DOCUMENT NUMBER: 138:117637
TITLE: Recombinant vesicular stomatitis virus (VSV) vector for the treatment of tumor cells
INVENTOR(S): Barber, Glen
PATENT ASSIGNEE(S): University of Miami, USA
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003005964	A2	20030123	WO 2002-US22146	20020711
WO 2003005964	A3	20030424		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2452517	AA	20030123	CA 2002-2452517	20020711
US 2003044386	A1	20030306	US 2002-194594	20020711
EP 1411880	A2	20040428	EP 2002-749985	20020711
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2004537305	T2	20041216	JP 2003-511773	20020711

PRIORITY APPLN. INFO.:

US 2001-304125P	P	20010711
WO 2002-US22146	W	20020711

AB The invention provides compns. and methods for the treatment of tumor and/or malignant and/or cancerous cells. The invention provides VSV vectors comprising nucleic acid encoding a cytokine, e..g interleukin or interferon, or a suicide gene, e.g. thymidine kinase, or other biol. protein, e.g. heat shock protein gp96, or endostatin or angiostatin, wherein the VSV vectors exhibit greater oncolytic activity against the tumor and/or malignant and/or cancerous cell than a wild-type VSV vector. The invention also provides methods of making such vectors, host cells, expression systems, and compns. comprising the VSV vectors, and viral particles comprising the VSV vectors. The invention further provides methods for producing oncolytic activity in a tumor and/or malignant and/or cancerous cell comprising contacting the cell with a VSV vector of the invention. The invention also provides methods for suppressing tumor growth comprising contacting the tumor with a VSV vector of the invention. The invention further provides methods for eliciting an immune response to a tumor cell in an individual.

L13 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:12214 CAPLUS
DOCUMENT NUMBER: 136:288667
TITLE: Genetically engineered vesicular stomatitis virus in gene therapy: application for treatment of malignant disease
AUTHOR(S): Fernandez, Marilyn; Porosnicu, Mercedes; Markovic, Dubravka; Barber, Glen N.
CORPORATE SOURCE: Department of Microbiology and Immunology and Sylvester Comprehensive Cancer Center, University of Miami School of Medicine, Miami, FL, 33136, USA
SOURCE: Journal of Virology (2002), 76(2), 895-904
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We report here the generation of recombinant vesicular stomatitis virus (VSV) able to produce the suicide gene product thymidine kinase (TK) or cytokine interleukin 4 (IL-4). In vitro cells infected with the engineered viruses expressed remarkably high levels of biol. active TK or IL-4 and showed no defects in replication compared to the wild-type virus. Recombinant viruses retained their ability to induce potent apoptosis in a variety of cancer cells, while normal cells were evidently more resistant to infection and were completely protected by interferon. Significantly, following direct intratumoral inoculation, VSV expressing either TK or IL-4 exhibited considerably more oncolytic activity against syngeneic breast or melanoma tumors in murine models than did the wild-type virus or control recombinant viruses expressing green fluorescent protein (GFP). Complete regression of a number of tumors was achieved, and increased granulocyte-infiltrating activity with concomitant, antitumor cytotoxic T-cell responses was observed Aside from discovering greater oncolytic activity following direct intratumoral inoculation, however, we also established that VSV expressing IL-4 or TK, but not GFP, was able to exert enhanced antitumor activity against metastatic disease. Following i.v. administration of the recombinant viruses, immunocompetent BALB/c mice inoculated with mammary adenocarcinoma exhibited prolonged survival against lethal lung metastasis. Our data demonstrate the validity of developing novel types of engineered VSV for recombinant protein production and as a gene therapy vector for the treatment of malignant and other disease.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:504637 CAPLUS
DOCUMENT NUMBER: 133:191813
TITLE: Exploiting tumor-specific defects in the interferon pathway with a previously unknown oncolytic virus
AUTHOR(S): Stojdl, David F.; Lichty, Brian; Knowles, Shane; Marius, Ricardo; Atkins, Harold; Sonenberg, Nahum; Bell, John C.
CORPORATE SOURCE: Ottawa Regional Cancer Centre Research Laboratories, Ottawa, ON, K1H 8L6, Can.
SOURCE: Nature Medicine (New York) (2000), 6(7), 821-825
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Interferons are circulating factors that bind to cell surface receptors, activating a signaling cascade, ultimately leading to both an antiviral response and an induction of growth inhibitory and/or apoptotic signals in normal and tumor cells. Attempts to exploit the

ability of interferons to limit the growth of tumors in patients has met with limited results because of cancer-specific mutations of gene products in the interferon pathway. Although interferon -non-responsive cancer cells may have acquired a growth/survival advantage over their normal counterparts, they may have simultaneously compromised their antiviral response. To test this, we used vesicular stomatitis virus (VSV), an enveloped, neg.-sense RNA virus exquisitely sensitive to treatment with interferon. VSV rapidly replicated in and selectively killed a variety of human tumor cell lines even in the presence of doses of interferon that completely protected normal human primary cell cultures. A single intratumoral injection of VSV was effective in reducing the tumor burden of nude mice bearing s.c. human melanoma xenografts. Our results support the use of VSV as a replication-competent oncolytic virus and demonstrate a new strategy for the treatment of interferon non-responsive tumors.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 12 OF 18 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2006:95255 BIOSIS
DOCUMENT NUMBER: PREV200600098446
TITLE: VSV-tumor selective replication and protein translation.
AUTHOR(S): Barber, Glen N. [Reprint Author]
CORPORATE SOURCE: Univ Miami, Sch Med, Dept Microbiol and Immunol, Sylvester Comprehens Canc Ctr, Room 511,Papanicolaou Bldg,1550 NW 10th St M710, Miami, FL 33136 USA
gbarber@med.miami.edu
SOURCE: Oncogene, (NOV 21 2005) Vol. 24, No. 52, pp. 7710-7719.
CODEN: ONCNES. ISSN: 0950-9232.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Feb 2006
Last Updated on STN: 1 Feb 2006

AB The emergence of vesicular stomatatis virus (VSV) as a potent antitumor agent has made a dissection of the molecular determinants of host-cell permissiveness to this virus an important objective. Such insight would not only enable the intelligent design of future generations of recombinant VSV vectors to combat disease, but may also resolve general features of cellular transformation that may be exploited by this virus, and perhaps other oncolytic viruses. The defective pathways underlining the oncolytic activity of VSV remain to be fully determined but recent data indicates that flaws in innate immune responses, involving the interferon (IFN) system, may commonly occur in tumor cells and thus play a large role in facilitating oncolysis. Aside from the IFN system, however, it is almost certain that other key cellular pathways may be similarly defective and therefore cooperatively contribute towards mediating rapid oncolytic virus activity. Recent data have indicated that defects in cancer cell translational regulation could be one area that may be exploited by VSV. Certainly, all viruses require cellular protein synthesis pathways to facilitate their replication and many have devised numerous mechanisms to ensure that viral mRNAs become translated at the expense of the host. Using VSV as a model, this review will discuss some of the recent developments in the fields of innate immunity and translational regulation that may help explain mechanisms of viral oncolysis.

L13 ANSWER 13 OF 18 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2006:39669 BIOSIS

DOCUMENT NUMBER: PREV200600039249
TITLE: Prophylactic alpha interferon treatment increases the therapeutic index of oncolytic vesicular stomatitis virus virotherapy for advanced hepatocellular carcinoma in immune-competent rats.
AUTHOR(S): Shinozaki, Katsunori; Ebert, Oliver; Suriawinata, Arief; Thung, Swan N.; Woo, Savio L. C. [Reprint Author]
CORPORATE SOURCE: Mt Sinai Sch Med, Dept Gene and Cell Med, 1 Gustave L Levy Pl,Box 1496, New York, NY 10029 USA
savio.woo@mssm.edu
SOURCE: Journal of Virology, (NOV 2005) Vol. 79, No. 21, pp. 13705-13713.
CODEN: JOVIAM. ISSN: 0022-538X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Dec 2005
Last Updated on STN: 28 Dec 2005

AB Vesicular stomatitis virus (VSV) is a negative-strand RNA virus with intrinsic oncolytic specificity due to substantially attenuated antiviral responses in many tumors. We have recently reported that recombinant VSV vector can be used as an effective oncolytic agent to safely treat multifocal hepatocellular carcinoma (HCC) in the livers of immune-competent rats via hepatic artery infusion. When administered at doses above the maximum tolerated dose (MTD), however, the animals suffered from neurotoxicity and/or acute lethal hepatotoxicity. Since VSV is extremely sensitive to the antiviral actions of alpha/beta interferon (IFN-alpha/beta) in normal cells, we tested if prophylactic treatment with rat IFN-alpha would enhance VSV safety without compromising treatment efficacy in tumor-bearing rats. We found that VSV retained its replication potential in human and rat HCC cells after preincubation with relatively high doses of rat and human IFN-alpha in vitro, and its MTD in tumor-bearing rats treated systemically with rat IFN-alpha at 66 IU/g body weight (BW), equivalent to a human IFN-alpha dose that is currently prescribed for patients with viral hepatitis, was elevated by more than 1/2 log unit. Furthermore, we demonstrate that intratumoral replication of VSV was not attenuated by administration of 66 IU/g BW rat IFN-alpha, as tumor response and survival advantage in VSV-treated rats in the presence or absence of rat IFN-alpha were equivalent. The results suggest that prophylactic rat IFN-alpha treatment elevates the therapeutic index of hepatic arterial VSV therapy for multifocal HCC in rats. Since human IFN-alpha is currently in clinical use, its prophylactic application should be considered in future clinical translational protocols for VSV-mediated oncolytic virotherapy as a novel therapeutic modality in patients with advanced HCC, as well as other types of cancer.

L13 ANSWER 14 OF 18 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:136795 BIOSIS
DOCUMENT NUMBER: PREV200500135625
TITLE: Vesicular stomatitis virus as an oncolytic vector.
AUTHOR(S): Barber, Glen N. [Reprint Author]
CORPORATE SOURCE: Sch MedSylvester Comprehens Canc CtrDept Microbiol and Immunol, Miami Univ, Rm 511 Papanicolaou Bldg,1550 NW 10th St M710, Miami, FL, 33136, USA
gbarber@med.miami.edu
SOURCE: Viral Immunology, (Winter 2004) Vol. 17, No. 4, pp. 516-527. print.
CODEN: VIIMET. ISSN: 0882-8245.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English

ENTRY DATE: Entered STN: 6 Apr 2005
Last Updated on STN: 6 Apr 2005

AB Recent data has shown that viruses such as vesicular stomatitis virus (VSV), a relatively non-pathogenic, negative-stranded RNA virus, can preferentially replicate in malignant cells and less so in normal cells. VSV appears able to carry out this function in transformed cells since these hosts exhibit the hallmarks of flawed host defense, probably involving the interferon system, which is essential for preventing virus replication. The simple genetic constitution of VSV, lack of any known transforming, integrating or reassortment properties, extensive knowledge relating to its interaction with the immune system and the ability to genetically manipulate this agent affords an ideal opportunity to exploit the oncolytic and gene targeting potential of this innocuous virus. Thus, aside from preferentially targeting malignant cells VSV recombinants could be generated that could increase a tumor's susceptibility to chemotherapeutic agents and/ or importantly, the host immune response. Collectively, our data and others demonstrate that VSV as well as other RNA viruses could provide a promising and exciting approach to cancer therapy.

L13 ANSWER 15 OF 18 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2005:82408 BIOSIS
DOCUMENT NUMBER: PREV200500076460
TITLE: Sensitivity of prostate tumors to wild type and M protein mutant vesicular stomatitis viruses.
AUTHOR(S): Ahmed, Maryam [Reprint Author]; Cramer, Scott D.; Lyles, Douglas S.
CORPORATE SOURCE: Sch MedDept Biochem, Wake Forest Univ, Med Ctr Blvd, Winston Salem, NC, 27157, USA
mahmed@wfubmc.edu
SOURCE: Virology, (December 5 2004) Vol. 330, No. 1, pp. 34-49. print.
ISSN: 0042-6822 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Feb 2005
Last Updated on STN: 23 Feb 2005

AB Because of its potent ability to induce apoptosis, vesicular stomatitis virus (VSV) is an attractive candidate as an oncolytic virus for tumor therapy. Previous studies have suggested that VSV selectively infects tumor cells due to defects in their antiviral responses making them more susceptible to VSV infection than normal cells. We tested this hypothesis in the prostate tumor system by comparing LNCaP and PC-3 prostate tumor cells to benign human prostatic epithelial cells from patient prostatectomy specimens. We compared the cell killing ability of a recombinant virus containing a wild-type (wt) M protein (rwt) and an isogenic M protein mutant virus (rM51R-M) that induces interferon (IFN) in infected cells and should display a greater selectivity for tumor cells. Our results showed that in single-cycle infection experiments, LNCaP cells were sensitive to killing by both wt and mutant viruses, while PC-3 cells were highly resistant to VSV-induced cell killing. LNCaP and benign prostate cells were similarly susceptible to both viruses, indicating that normal prostate cells are not inherently resistant to killing by VSV. In each of the cell lines, the rM51R-M virus induced similar levels of apoptosis to rwt virus, showing that the M protein does not play a significant role in apoptosis induction by VSV in these cells. In multiple-cycle infection experiments, LNCaP cells were more sensitive than benign prostatic epithelial cells to virus-induced cell killing by rM51R-M virus, but not rwt virus. Both viruses were equally effective at reducing LNCaP tumor volume in vivo following intratumoral and intravenous inoculation in nude mice, while PC-3 tumors were resistant to VSV treatment.

None of the mice treated with rM51R-M virus died as a result of virus infection, while 50-71% of mice treated with rwt virus succumbed to virus infection. Similarly, when inoculated by the more sensitive intranasal route, the rM51R-M virus was less pathogenic than the rwt virus from which it was derived. These results indicate that M protein mutant viruses are superior candidates as oncolytic viruses for therapies of prostate tumors, but future strategies for use of VSV will require testing individual tumors for their susceptibility to virus infection.

L13 ANSWER 16 OF 18 BIOSIS on STN

ACCESSION NUMBER: 2003:432731 BIOSIS
DOCUMENT NUMBER: PREV200300432731
TITLE: Development of recombinant vesicular stomatitis viruses that exploit defects in host defense to augment specific oncolytic activity.
AUTHOR(S): Obuchi, Masatsugu; Fernandez, Marilyn; Barber, Glen N. [Reprint Author]
CORPORATE SOURCE: University of Miami School of Medicine, 1550 NW 10th Ave., Rm. 511, Papanicolaou Building, M710, Miami, FL, 33136, USA gbarber@med.miami.edu
SOURCE: Journal of Virology, (August 2003) Vol. 77, No. 16, pp. 8843-8856. print.
ISSN: 0022-538X (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Sep 2003
Last Updated on STN: 17 Sep 2003

AB Vesicular stomatitis virus (VSV) is a negative-stranded RNA virus normally sensitive to the antiviral actions of alpha/beta interferon (IFN-alpha/beta). Recently, we reported that VSV replicates to high levels in many transformed cells due, in part, to susceptible cells harboring defects in the IFN system. These observations were exploited to demonstrate that VSV can be used as a viral oncolytic agent to eradicate malignant cells in vivo while leaving normal tissue relatively unaffected. To attempt to improve the specificity and efficacy of this system as a potential tool in gene therapy and against malignant disease, we have genetically engineered VSV that expresses the murine IFN-beta gene. The resultant virus (VSV-IFNbeta) was successfully propagated in cells not receptive to murine IFN-alpha/beta and expressed high levels of functional heterologous IFN-beta. In normal murine embryonic fibroblasts (MEFs), the growth of VSV-IFNbeta was greatly reduced and diminished cytopathic effect was observed due to the production of recombinant IFN-beta, which by functioning in a manner involving autocrine and paracrine mechanisms induced an antiviral effect, preventing virus growth. However, VSV-IFNbeta grew to high levels and induced the rapid apoptosis of transformed cells due to defective IFN pathways being prevalent and thus unable to initiate proficient IFN-mediated host defense. Importantly, VSV expressing the human IFN-beta gene (VSV-hIFNbeta) behaved comparably and, while nonlytic to normal human cells, readily killed their malignant counterparts. Similar to our in vitro observations, following intravenous and intranasal inoculation in mice, recombinant VSV (rVSV)-IFNbeta was also significantly attenuated compared to wild-type VSV or rVSV expressing green fluorescent protein. However, VSV-IFNbeta retained propitious oncolytic activity against metastatic lung disease in immunocompetent animals and was able to generate robust antitumor T-cell responses. Our data indicate that rVSV designed to exploit defects in mechanisms of host defense can provide the basis for new generations of effective, specific, and safer viral vectors for the treatment of malignant and other disease.

L13 ANSWER 17 OF 18 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:143666 BIOSIS
DOCUMENT NUMBER: PREV200200143666
TITLE: Genetically engineered vesicular stomatitis virus in gene therapy: Application for treatment of malignant disease.
AUTHOR(S): Fernandez, Marilyn; Porosnicu, Mercedes; Markovic, Dubravka; Barber, Glen N. [Reprint author]
CORPORATE SOURCE: University of Miami School of Medicine, 1550 NW 10th Ave., Rm. 511, Papanicolaou Building, M710, Miami, FL, 33136, USA gbarber@med.miami.edu
SOURCE: Journal of Virology, (January, 2002) Vol. 76, No. 2, pp. 895-904. print.
CODEN: JOVIAM. ISSN: 0022-538X.
DOCUMENT TYPE: Article
LANGUAGE: English
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AB We report here the generation of recombinant vesicular stomatitis virus (VSV) able to produce the suicide gene product thymidine kinase (TK) or cytokine interleukin 4 (IL-4). In vitro cells infected with the engineered viruses expressed remarkably high levels of biologically active TK or IL-4 and showed no defects in replication compared to the wild-type virus. Recombinant viruses retained their ability to induce potent apoptosis in a variety of cancer cells, while normal cells were evidently more resistant to infection and were completely protected by interferon. Significantly, following direct intratumoral inoculation, VSV expressing either TK or IL-4 exhibited considerably more oncolytic activity against syngeneic breast or melanoma tumors in murine models than did the wild-type virus or control recombinant viruses expressing green fluorescent protein (GFP). Complete regression of a number of tumors was achieved, and increased granulocyte-infiltrating activity with concomitant, antitumor cytotoxic T-cell responses was observed. Aside from discovering greater oncolytic activity following direct intratumoral inoculation, however, we also established that VSV expressing IL-4 or TK, but not GFP, was able to exert enhanced antitumor activity against metastatic disease. Following intravenous administration of the recombinant viruses, immunocompetent BALB/c mice inoculated with mammary adenocarcinoma exhibited prolonged survival against lethal lung metastasis. Our data demonstrate the validity of developing novel types of engineered VSV for recombinant protein production and as a gene therapy vector for the treatment of malignant and other disease.

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AB Interferons are circulating factors that bind to cell surface receptors, activating a signaling cascade, ultimately leading to both an

antiviral response and an induction of growth inhibitory and/or apoptotic signals in normal and tumor cells. Attempts to exploit the ability of interferons to limit the growth of tumors in patients has met with limited results because of cancer-specific mutations of gene products in the interferon pathway. Although interferon -non-responsive cancer cells may have acquired a growth/survival advantage over their normal counterparts, they may have simultaneously compromised their antiviral response. To test this, we used vesicular stomatitis virus (VSV), an enveloped, negative-sense RNA virus exquisitely sensitive to treatment with interferon. VSV rapidly replicated in and selectively killed a variety of human tumor cell lines even in the presence of doses of interferon that completely protected normal human primary cell cultures. A single intratumoral injection of VSV was effective in reducing the tumor burden of nude mice bearing subcutaneous human melanoma xenografts. Our results support the use of VSV as a replication-competent oncolytic virus and demonstrate a new strategy for the treatment of interferon non-responsive tumors.